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Review

# Transcranial magnetic stimulation as a tool for understanding neurophysiology in Huntington's disease: A review

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ABSTRACT

Structural and functional magnetic resonance imaging modalities have been critical in advancing our understanding of the neuroanatomical and pathophysiological changes that emerge during the premanifest and symptomatic stages of Huntington's disease (HD). However, the relationship between underlying neuropathology and the motor, cognitive and behavioural changes associated with the disorder still remain poorly understood. Less conventional technologies, such as transcranial magnetic stimulation (TMS) and electroencephalography (EEG), provide a unique opportunity to further investigate the causal relationships between targeted neural circuits and objective neurophysiological responses together with overt behaviours. In this review, we discuss previous successful applications of TMS in other neurological disorders and its prospective use in HD. We also address the added value of multimodal TMS techniques, such as TMS–EEG, in investigating the integrity of neural networks in non-motor regions in HD. We conclude that neurophysiological outcome measures are likely to contribute towards characterising further the trajectory of decline across functional domains in HD, enhance understanding of underlying neural mechanisms, and offer new avenues for elucidating sensitive endophenotypic biomarkers of disease progression.



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## 1. Overview

Gamma amino-butyric acid (GABA) is the most common inhibitory neurotransmitter in mammalian nervous systems, and is widespread in cortical and subcortical regions (Davies et al., 1990). In the cortex, cortical inhibition occurs primarily via GABAergic inhibitory interneurons, which modulate the output of other cortical neurons (Fitzgerald et al., 2008; Krnjevic, 1997). The basal ganglia (BG) also use GABA as their primary neurotransmitter to regulate cortical activity (Parent and Hazrati, 1995). The principal input site to the BG is the striatum, comprising the caudate nucleus and putamen, while the output is driven by excitatory 'corticostriatal' projections from the thalamus to the cerebral cortex (Cepeda et al., 2007). Alterations to this corticostriatal circuitry may result in widespread functional impairments, known to cause a complex presentation of motor and cognitive deficits in neurodegenerative disorders, such as Huntington's (HD) and Parkinson's (PD) diseases (Albin et al., 1989; Di Martino et al., 2008; Saint-Cyr, 2003). While HD will be the main focus of this review, PD, which is caused by selective loss of dopamine-producing neurons in the substantia nigra, affords an important comparison in terms of BG dysfunction (Joel, 2001).

Magnetic resonance imaging (MRI) and positron emission tomography (PET) technologies have been critical in driving forward our understanding of the underlying neuropathology in such disorders. Recent advances in other cutting-edge neurophysiological modalities, including transcranial magnetic stimulation (TMS), promise to provide unique insights into the complex relationship between symptomatology and underlying pathophysiology in clinical populations. We review the existing neuroimaging and neurocognitive/motor literature and examine how outcomes from such studies have informed our current understanding of the premanifest and symptomatic expression of HD. We then focus our review on TMS and electroencephalography (EEG) methods and their capacity to offer new and exciting opportunities to further enhance knowledge relating to the complex biobehavioural relationships underlying the neuroanatomical and pathophysiological abnormalities, as well as the cognitive, motor and behavioural disturbances that characterise HD.

## 2. Huntington's disease

### 2.1. Genetics and neuropathology

HD is an inherited neurodegenerative disorder caused by pathological expansion of the triplet CAG repeat in the IT15 gene coding for the protein 'huntingtin' (Huntington's Disease Collaborative Research Group, 1993; Vonsattel and DiFiglia, 1998). HD is characterised by a triad of symptoms comprising motor, cognitive and psychiatric disturbances (Huntington's Disease Collaborative Research Group, 1996) and clinical diagnosis is obtained once motor symptoms reach a threshold level of severity via the Unified Huntington's Disease Rating Scale (UHDRS; Huntington's Disease Collaborative Research Group, 1996). The age of clinical onset can be estimated using a simple formula that can predict, with up to 50% certainty, the likely timing of symptom onset based on CAG repeat and current age (Langbehn et al., 2004).

The striatum is the primary site of HD pathology (Albin et al., 1992; De La Monte et al., 1988; Diamond et al., 1992; Grafton et al., 1992), with preferential loss of medium spiny GABAergic neurons occurring first in the caudate and then the putamen (Andrews et al., 1999; Douaud et al., 2009; Sapp et al., 1997; Vonsattel and DiFiglia, 1998). Although BG circuitry is complex, the result of striatal atrophy is essentially under-inhibition of the thalamus and consequently over-excitation of cerebral cortex via glutamatergic excitatory thalamic projections (Aron et al., 2003). HD pathology is associated with abnormal neurotransmitter regulation and synaptic communication, as well as glutamate-mediated excitotoxicity and down-regulation of brain-derived neurotrophic factor (Centonze et al., 2005; Cepeda et al., 2003, 2004; Cha et al., 1998; Cummings et al., 2009; DiProspero et al., 2004; Hodgson et al., 1999; Klapstein et al., 2001; Storey et al., 1992; Zuccato et al., 2001). There is considerable evidence supporting a cascade of biochemical abnormalities resulting in numerous morphological cell changes, both degenerative and compensatory, that the HD brain undergoes prior to notable cell loss.

### 2.2. Overview of neuroimaging findings and functional neuroanatomy

A wealth of research has established that striatal structural changes in HD can be detected up to 15–20 years prior to clinical diagnosis (Bohanna et al., 2011a; Georgiou-Karistianis et al., 2013a; Jurgens et al., 2008; Mascalchi et al., 2004; Sánchez-Castañeda et al., 2012; Thieben et al., 2002). PREDICT-HD (Paulsen et al., 2008) and TRACK-HD (Tabrizi et al., 2009) are two large-scale multi-site longitudinal studies reporting strong effect sizes for neuroimaging measures in the very early premanifest, or 'pre-HD', stages of HD. As part of PREDICT-HD, Paulsen et al. (2010) demonstrated stepwise volumetric changes in individuals more than 15 years before estimated onset, not only in subcortical regions, but also in cortical grey matter (GM), cerebral white matter (WM) and total brain tissue. Furthermore, in TRACK-HD, Tabrizi et al. (2011, 2012) showed stepwise increased rates of change in caudate and putamen from pre-HD through to early and late stages of functional impairment, and highly significant correlations between rate of change in these structures and disease burden scores. To date, however, there are no studies that have examined correlations between longitudinal change in MRI volumetric measures and longitudinal change in measures of disease progression (for a review see Georgiou-Karistianis et al., 2013b).

Regionally-selective cortical thinning in symptomatic HD ('symp-HD'), and pre-HD has also been well-established (Georgiou-Karistianis et al., 2013b; Gómez-Ansón et al., 2009; Nopoulos et al., 2010; Rosas et al., 2002, 2005; Stoffers et al., 2010; Tabrizi et al., 2009). Variations in patterns of cortical thinning have been linked to specific phenotypes in HD and it is possible that these measures may be useful in understanding the heterogeneity in clinical presentation (Rosas et al., 2008b, 2011). PREDICT-HD has established that morphologic changes in cortical GM occur later in the disease process with WM changes seen early (Aylward et al., 2011; Nopoulos et al., 2010). Furthermore, methods such as diffusion tensor imaging (DTI) have revealed widespread microstructural changes in cortical and subcortical regions, which parallel earlier macrostructural findings. Alterations in mean diffusivity (MD)